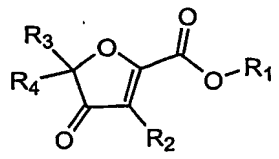
CLAIMS

We claim:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, hydrate or solvate thereof,

wherein:

R_1 is H or C_{1-6} alkyl;

R_2 is H, halogen, C_{1-4} alkyl or C_{1-4} haloalkyl; and

A) R_3 is aryl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, heteroaryl, C_{3-7} heterocycloalkyl or C_{3-7} heterocycloalkenyl wherein each are optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, amino, aryl, substituted aryl, carbo-C_{1-6}-alkoxy, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, heteroaryl, substituted heteroaryl, hydroxyl, nitro and thiol; and

R_4 is selected from the group consisting of H, ethyl, n-propyl, C_{4-6} alkyl and C_{1-6} haloalkyl wherein each are optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, amino, carbo-C_{1-6}-alkoxy, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol; or

R_4 is C_{3-6}-cycloalkyl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, amino, carbo-C_{1-6}-alkoxy, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol;

or

B) R_3 is a substituted phenyl, 2-chlorophenyl, 3-chlorophenyl, naphthyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, heteroaryl, C_{3-7} heterocycloalkyl or C_{3-7} heterocycloalkenyl wherein

said 2-chlorophenyl, 3-chlorophenyl, naphthyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, heteroaryl, C_{3-7} heterocycloalkyl and C_{3-7} heterocycloalkenyl are optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, amino, aryl, substituted aryl, carbo-C_{1-6}-alkoxy, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, heteroaryl, substituted heteroaryl, hydroxyl, nitro and thiol; and

R_4 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-6}-cycloalkyl and C_{1-6} haloalkyl wherein each are optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamide, C_{2-6} alkynyl, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, amino, carbo-C_{1-6}-alkoxy, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

2. The compound according to claim 1 wherein R_1 is C_{1-6} alkyl.

3. The compound according to claim 1 wherein R_1 is methyl or ethyl.

4. The compound according to claim 1 wherein R_1 is H.

5. The compound according to any one of claims 1 to 4 wherein R_2 is H.

6. The compound according to any one of claims 1 to 5 wherein R_4 is C_{1-6} alkyl.

7. The compound according to any one of claims 1 to 5 wherein R_4 is methyl.

8. The compound according to any one of claims 1 to 5 wherein R_4 is ethyl.

9. The compound according to any one of claims 1 to 5 wherein R_4 is C_{1-6} haloalkyl.

10. The compound according to any one of claims 1 to 5 wherein R_4 is trifluoromethyl.

11. The compound according to any one of claims 1 to 10 wherein R_3 is substituted phenyl, 3-chlorophenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl or heteroaryl, wherein said 3-chlorophenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl and heteroaryl are optionally substituted with 1 to 5 substituents

selected from the group consisting of C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl, cyano, halogen, C_{1-6} haloalkyl and heteroaryl.

12. The compound according to any one of claims 1 to 10 wherein R_3 is thienyl optionally substituted with C_{1-6} alkyl, halogen or C_{1-6} haloalkyl.

13. The compound according to any one of claims 1 to 10 wherein R_3 is thienyl optionally substituted with methyl, ethyl, F, Cl, Br, I or trifluoromethyl.

14. The compound according to any one of claims 1 to 10 wherein R_3 is selected from the group consisting of biphenyl-3-yl, 3-thiophen-2-yl-phenyl, 3-bromo-phenyl, 3-iodo-phenyl, 3-chloro-phenyl, 3-fluoro-phenyl, 3,5-difluoro-phenyl, m-tolyl, 3-ethyl-phenyl, 3-trifluoromethyl-phenyl, 4-fluoro-phenyl, 2-fluoro-phenyl, 3,4-difluoro-phenyl, 2,4-difluoro-phenyl, 2,6-difluoro-phenyl, 2,5-dichloro-phenyl, 3-methoxy-phenyl, 3,5-dichloro-phenyl, 3-cyano-phenyl, 3-propenyl-phenyl, 3-hex-1-enyl-phenyl and 3-vinyl-phenyl.

15. The compound according to any one of claims 1 to 10 wherein R_3 is selected from the group consisting of thiophen-3-yl, thiophen-2-yl, 4-bromo-thiophen-2-yl, 5-methyl-thiophen-2-yl, 5-chloro-thiophen-2-yl, 5-bromo-thiophen-3-yl, 5-chloro-thiophen-3-yl, 4-bromo-5-methyl-thiophen-2-yl, pyridin-3-yl, furan-2-yl, 4-methyl-thiophen-2-yl and 5-methyl-thiophen-3-yl.

16. The compound according to any one of claims 1 to 10 wherein R_3 is selected from the group consisting of cyclohex-1-enyl, cyclopent-1-enyl and cyclopentyl.

17. The compound according to claim 1 wherein:

R_1 is H;

R_2 is H;

R_4 is C_{1-6} alkyl or C_{1-6} haloalkyl; and

R_3 is substituted phenyl, 3-chlorophenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl or heteroaryl, wherein said 3-chlorophenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl, cyano, halogen, C_{1-6} haloalkyl and heteroaryl.

18. The compound according to claim 1 wherein:

R_1 is H;

R_2 is H;

R_4 is methyl, ethyl or trifluoromethyl; and

R_3 is selected from the group consisting of biphenyl-3-yl, 3-thiophen-2-yl-phenyl, 3-bromo-phenyl, 3-iodo-phenyl, 3-chloro-phenyl, 3-fluoro-phenyl, 3,5-difluoro-phenyl, m-tolyl, 3-ethyl-phenyl, 3-trifluoromethyl-phenyl, 3,4-difluoro-phenyl, 2,4-difluoro-phenyl, 2,6-difluoro-phenyl, 2,5-dichloro-phenyl, 3-methoxy-phenyl, 3,5-dichloro-phenyl, 3-cyano-phenyl, 3-propenyl-phenyl, 3-hex-1-enyl-phenyl and 3-vinyl-phenyl.

19. The compound according to claim 1 wherein:

R_1 is H;

R_2 is H;

R_4 is methyl, ethyl or trifluoromethyl; and

R_3 is thienyl optionally substituted with C_{1-6} alkyl or halogen.

20. The compound according to claim 1 wherein:

R_1 is H;

R_2 is H;

R_4 is methyl, ethyl or trifluoromethyl; and

R_3 is selected from the group consisting of thiophen-3-yl, thiophen-2-yl, 4-bromo-thiophen-2-yl, 5-methyl-thiophen-2-yl, 5-chloro-thiophen-2-yl, 5-bromo-thiophen-3-yl, 5-chloro-thiophen-3-yl, 4-bromo-5-methyl-thiophen-2-yl, pyridin-3-yl, furan-2-yl, 4-methyl-thiophen-2-yl and 5-methyl-thiophen-3-yl.

21. The compound according to claim 1 selected from the group consisting of:

5-Cyclohex-1-enyl-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;

5-Methyl-4-oxo-5-thiophen-3-yl-4,5-dihydro-furan-2-carboxylic acid methyl ester;

5-Methyl-4-oxo-5-thiophen-2-yl-4,5-dihydro-furan-2-carboxylic acid methyl ester;

5-(4-Bromo-thiophen-2-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;

5-(4-Bromo-thiophen-2-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;

5-Methyl-5-(5-methyl-thiophen-2-yl)-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;

5-Methyl-5-(5-methyl-thiophen-2-yl)-4-oxo-4,5-dihydro-furan-2-carboxylic acid;

5-(5-Chloro-thiophen-2-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl; ester;

5-Cyclopent-1-enyl-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;

5-Biphenyl-3-yl-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;

5-Methyl-4-oxo-5-(3-thiophen-2-yl-phenyl)-4,5-dihydro-furan-2-carboxylic acid methyl ester;

5-(3-Bromo-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;

5-(3-Bromo-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(3-Iodo-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(3-Chloro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(3-Fluoro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(3,5-Difluoro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-4-oxo-5-m-tolyl-4,5-dihydro-furan-2-carboxylic acid;
5-(3-Ethyl-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-4-oxo-5-(3-trifluoromethyl-phenyl)-4,5-dihydro-furan-2-carboxylic acid;
5-(5-Chloro-thiophen-2-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid; and
5-Methyl-4-oxo-5-thiophen-2-yl-4,5-dihydro-furan-2-carboxylic acid; or
a pharmaceutically acceptable salt, hydrate or solvate thereof.

22. The compound according to claim 1 selected from the group consisting of:
5-(5-Bromo-thiophen-3-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-(5-Bromo-thiophen-3-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(5-Chloro-thiophen-3-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-(5-Chloro-thiophen-3-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(4-Bromo-5-methyl-thiophen-2-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-4-oxo-5-thiophen-3-yl-4,5-dihydro-furan-2-carboxylic acid;
5-(4-Fluoro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-4-oxo-5-pyridin-3-yl-4,5-dihydro-furan-2-carboxylic acid;
5-Ethyl-4-oxo-5-phenyl-4,5-dihydro-furan-2-carboxylic acid;
5-(2-Fluoro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
2-Methyl-3-oxo-2,3-dihydro-[2,2']bifuranyl-5-carboxylic acid;
5-(3,4-Difluoro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(2,4-Difluoro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(2,6-Difluoro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(2,5-Dichloro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(3-Methoxy-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-4-oxo-5-m-tolyl-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-(3-Ethyl-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-Cyclohex-1-enyl-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-(3,5-Dichloro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-(3,5-Dichloro-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;

5-(3-Iodo-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-Cyclopentyl-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-Cyclopentyl-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-(3-Cyano-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-(3-Cyano-phenyl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-4-oxo-5-[3-propenyl)-phenyl]-4,5-dihydro-furan-2-carboxylic acid;
5-(4-Bromo-5-methyl-thiophen-2-yl)-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-Biphenyl-3-yl-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-[3-Hex-1-enyl)-phenyl]-5-methyl-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-5-(4-methyl-thiophen-2-yl)-4-oxo-4,5-dihydro-furan-2-carboxylic acid methyl ester;
5-Methyl-4-oxo-5-(3-vinyl-phenyl)-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-5-(4-methyl-thiophen-2-yl)-4-oxo-4,5-dihydro-furan-2-carboxylic acid;
5-Methyl-5-(5-methyl-thiophen-3-yl)-4-oxo-4,5-dihydro-furan-2-carboxylic acid; and
4-Oxo-5-phenyl-5-trifluoromethyl-4,5-dihydro-furan-2-carboxylic acid; or
a pharmaceutically acceptable salt, hydrate or solvate thereof.

23. The compound according to any one of claims 1 to 22 wherein said compound is essentially the R enantiomer.

24. The compound according to any one of claims 1 to 22 wherein said compound is essentially the S enantiomer.

25. A pharmaceutical composition comprising a compound according to any one of claims 1 to 24 in combination with a pharmaceutically acceptable carrier.

26. A pharmaceutical composition according to claim 25 further comprising an agent selected from the group consisting of α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

27. A method of treatment of a metabolic-related disorder comprising administering to an individual in need of such treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 24 or a pharmaceutical composition of claim 25 or 26.

28. The method according to claim 27 wherein said metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity,

impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes.

29. The method according to claim 27 wherein said metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

30. The method according to claim 27 wherein said metabolic-related disorder is atherosclerosis.

31. A method of modulating a RUP25 receptor comprising contacting said receptor with a compound according to any one of claims 1 to 24 or a pharmaceutical composition of claim 25 or 26.

32. A method of modulating a RUP25 receptor for the treatment of a metabolic-related disorder in an individual in need of such modulation comprising contacting said receptor with a therapeutically-effective amount of a compound according to any one of claims 1 to 24 or a pharmaceutical composition of claim 25 or 26.

33. The method according to claim 31 or 32 wherein said compound is an agonist.

34. The method according to claim 33 wherein said agonist is a partial agonist.

35. A method of raising HDL in an individual comprising administering to said individual a therapeutically-effective amount of a compound according to any one of claims 1 to 24 or a pharmaceutical composition of claim 25 or 26.

36. The method according to any one of claims 27 to 35 wherein said individual is a mammal.

37. The method according to claim 36 wherein said mammal is a human.

38. A compound according to any one of claims 1 to 24 for use in a method of treatment of the human or animal body by therapy.

39. A compound according to any one of claims 1 to 24 for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy.

40. A compound according to any one of claims 1 to 24 for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy wherein said metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart

disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes.

41. A compound according to any one of claims 1 to 24 for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy wherein said metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

42. A compound according to any one of claims 1 to 24 for use in a method of treatment of atherosclerosis of the human or animal body by therapy.

43. A compound according to any one of claims 1 to 24 for use in a method of raising HDL of the human or animal body by therapy.

44. Use of a compound according to any one of claims 1 to 24 for the manufacture of a medicament for use in the treatment of a metabolic-related disorder.

45. Use of a compound according to any one of claims 1 to 24 for the manufacture of a medicament for use in the treatment of a metabolic-related disorder selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes.

46. Use of a compound according to any one of claims 1 to 24 for the manufacture of a medicament for use in the treatment of atherosclerosis.

47. Use of a compound according to any one of claims 1 to 24 for the manufacture of a medicament for use in raising HDL in an individual.

48. A method of producing a pharmaceutical composition comprising admixing a compound according to any one of claims 1 to 24 and a pharmaceutically acceptable carrier.